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ScienceDirect

Journal of Electrocardiology xx (2014) xxx – xxx

JOURNAL OF Electrocardiology

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The effect of obstructive sleep apnea on QRS complex morphology

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Abstract

Background: Obstructive sleep apnea (OSA) has been reported to be associated with an increased risk of ventricular arrhythmias and conduction disturbances. The aim of this study was to analyze the QRS complex morphology potentially indicative of intraventricular conduction impairment in patients with mild to severe OSA.

Material and methods: One hundred ninety-three consecutive patients, who underwent complete overnight polysomnography, were divided into four groups based on the OSA severity: (1) no OSA, (2) mild OSA, (3) moderate OSA and (4) severe OSA (apnea-hypopnea index <5, 5–15, 15–30, >30/h, respectively). Resting 12-lead ECG was recorded, the QRS parameters included QRS amplitude in individual leads, QRS spatial vector magnitude (QRSmax), electrical axis (EA), ECG criteria for left ventricular hypertrophy (ECG-LVH) and right ventricular hypertrophy (ECG-RVH), and occurrence of fragmented QRS (fQRS).

Results: Severity of OSA was significantly associated with a gradual significant shift of the electrical axis to the left (45.5 ± 22.5°; 34.8 ± 17.1°; 32.9 ± 18.2°; 29.8 ± 10.0°; respectively), while the QRSmax values were low in all patient groups, with a significant difference between no OSA and severe OSA groups. The multivariate analysis showed that QRSmax was independently associated with age and the interaction between gender and OSA severity ($p = 0.001$, and $p = 0.004$, respectively; adjusted $R^2 = 0.178$). The electrical axis was found to be independently associated with age and OSA severity ($p = 0.037$, and $p = 0.026$, respectively; $R^2 = 0.109$). Changes of electrical axis and of QRSmax were reflected in corresponding changes in the amplitude of 12-lead ECG and in low occurrence of ECG-LVH and ECG-RVH criteria. The OSA groups had higher occurrence of fQRS.

Conclusion: OSA patients displayed a combination of changes in QRS complex morphology, the leftward shift of EA, low QRS voltage and fQRS, suggestive of depolarization sequence deterioration that might be indicative of considerable electrical remodeling.

Keywords: Sleep apnea; QRS complex; QRS voltage; Electrical axis; Fragmented QRS complex

Introduction

Obstructive sleep apnea (OSA) is a sleep disordered breathing caused by obstruction in the upper airway leading to repetitive episodes of hypoxia and reoxygenation [1,2]. It is frequently associated with additional co-morbidities, such as obesity, hypertension, insulin resistance, metabolic syndrome, and chronic obstructive pulmonary disease, which may be instrumental in creating conditions for ventricular arrhythmias including ventricular fibrillation [3–5]. Recognition of ECG changes suggestive of electrical remodeling in OSA patients is therefore of clinical importance.

In the standard 12-lead ECG, the regional conductions barriers/electrical heterogeneity can be manifested as a fragmented QRS complex [6,7], and the slowed intraventricular conduction/delayed ventricular activation as a prolonged QRS complex [8]. Additionally, in our simulation studies we have shown that changes in ventricular activation affect considerably also the QRS complex morphology, including QRS amplitude and electrical axis [9–11]. In a clinical study [12] we documented the decrease in QRS amplitude and left axis deviation in patients with metabolic

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http://dx.doi.org/10.1016/j.jelectrocard.2014.12.007
0022-0736/

syndrome (MetS) or diabetes mellitus (DM), these changes in less pronounced manner were present even in the clinically healthy offspring of MetS and DM patients. We concluded that these subtle changes could be indicative of early intraventricular activation alterations/electrical remodeling.

The aim of this study was to analyze the QRS complex morphology indicative of intraventricular conduction impairment in patients with mild to severe OSA.

Material and methods

Study population

Subjects without OSA (<5 obstructive apneas or hypopneas per hour of sleep), and patients with OSA (≥5 obstructive apneas or hypopneas per hour of sleep and excessive daytime sleepiness) referred to the sleep unit at a tertiary referral teaching hospital for a diagnostic sleep study due to snoring and daytime sleepiness were prospectively recruited within the Project APVV-0134–11 Effects of Hypoxia on Molecular Pathways related to Increased Cardiovascular Risk in Patients with Sleep Apnea and their Reversal by Therapy (HICART).

Patients with chronic respiratory diseases other than OSA, such as central sleep apnea, bronchial asthma, chronic obstructive pulmonary disease, restrictive pulmonary disorders or hypoventilation syndrome, as well as with incomplete data and left bundle branch block pattern on ECG were excluded from the study.

The study had local ethics committee approval, and all subjects provided written informed consent.

Sleep assessment

All participants underwent full attended diagnostic overnight polysomnography (Alice 4, Respironics Inc., Murrysville, PA, USA), comprising continuous recording of electroencephalography, electrooculography, electromyography, electrocardiography, thoracic and abdominal impedance belts, thermistor for nasal and oral airflow, pulse oximetry, and microphone for snoring. The parameters, settings, filters, technical specifications, manual sleep stage scoring and manual events scoring were performed by qualified sleep technicians and reviewed by respirologists trained in sleep medicine in accordance with the Rules for Scoring Respiratory Events in Sleep: Update from the 2007, AASM Manual for the Scoring of Sleep and Associated Events [13]. Apnea was identified as a drop in airflow of >90% from the baseline excursion for ≥10 seconds; hypopnea was defined as a reduction in airflow of at least 50% of baseline for ≥10 seconds, accompanied either by a decrease in hemoglobin saturation for ≥3%, an EEG-recorded arousal, or both. The apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The oxygen desaturation index (ODI) was defined as the number of oxygen desaturations of hemoglobin of ≥3% per hour of sleep. In addition, time of transcutaneous oxygen saturation below 90% (SpO_2 <90%) was also used to assess the degree of nocturnal hypoxia. The classification of OSA severity was based on the AASM guidelines [13] as follows: mild: AHI ≥5 and <15 episodes/hour; moderate: AHI ≥15 and <30 episodes/hour; and severe OSA: AHI ≥30 episodes/hour.

The total number of 193 patients was divided into four groups:

- Group I (no OSA, AHI <5 episodes/hour): n = 22, (14/8 F/M), average age 43.3 years (range 24–66)
- Group II (mild OSA, AHI ≥5 and < 15 episodes/hour): n = 46, (20/26 F/M), average age 53.4 years (range 23–80)
- Group III (moderate OSA, AHI ≥15 and <30 episodes/hour): n = 26, (10/16 F/M), average age 53.0 years (range 30–80)
- Group IV (severe OSA, AHI ≥30 episodes/hour): n = 99, (15/84 F/M), average age 56.2 years (range 29–78).

The basic characteristics of the study population are presented in Table 1.

Table 1
Basic characteristics and polysomnographic findings of the study groups.

	No OSA n = 22	Mild OSA n = 46	Moderate OSA n = 26	Severe OSA n = 99
Gender, n (%)				
Male	8 (36.4)	26 (56.5)	16 (61.5)	84 (84.8)
Female	14 (63.6)	20 (43.5)	10 (38.5)	15 (15.2)
Age, y	43.3 (10.5)	53.4 (11.7)*	53.0 (10.3)*	56.2 (10.0)*
BMI, $kg \cdot m^{-2}$	27.7 (4.5)	29.8 (4.8)	31.5 (5.4)*	35.3 (5.9)*
Systolic BP, mm Hg	120.2 (15.5)	122.7 (16.3)	130.0 (17.5)	137.9 (16.9)*
Diastolic BP, mm Hg	79.1 (10.1)	80.8 (10.1)	82.5 (11.4)	87.2 (8.5)*
Glucose, mml/l	4.7 (0.5)	5.0 (1.1)	4.9 (0.8)	5.8 (1.8)*
Cholesterol, mmol/l	4.8 (0.4)	5.1 (1.0)	5.2 (1.1)	5.1 (1.1)
Triglyceride, mmol/l	1.30 (0.81)	1.51 (0.71)	1.91 (1.12)*	2.13 (1.26)*
History of hypertension, n (%)	11 (50)	21 (46)	19 (73)	79 (80)
History of type 2 diabetes, n (%)	0 (0)	4 (9)	5 (19)	16 (16)
AHI, $n \cdot h^{-1}$	3.0 (1.3)	10.3 (2.8)*	21.2 (3.6)*	64.1 (22.3)*
ODI, $n \cdot h^{-1}$	2.0 (9.6)	7.5 (3.7)*	17.6 (7.6)*	57.8 (24.9)*
SpO_2 below 90%, min	0.5 (1.2)	3.7 (8.9)	8.4 (18.2)	102.9 (105.2)*
Lowest SpO_2, %	90.1 (7.3)	85.9 (5.7)*	83.7 (7.4)*	69.5 (15.7)*

BMI: body mass index; BP: blood pressure; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO2: pulse oximetric saturation.
* $p < 0.05$ as compared to no OSA group.

Electrocardiography

The standard 12-lead electrocardiograms were recorded using a Marquette Centra electrocardiograph. The amplitudes of the QRS waves in individual leads were measured manually, each ECG record was evaluated by two blinded ECG readers. In a case of disagreements, the third expert was involved.

ECG parameters analyzed:

- xThe maximum spatial vector magnitude (QRSmax) calculated as:

$$QRS_{max} = \sqrt{V2^2 + aVF^2 + V5^2}$$

where V2 is the maximum QRS deflection in lead V2; aVF is the maximum QRS deflection in lead aVF; V5 is the maximum QRS deflection in lead V5.

- The electrical QRS axis (EA) was calculated as:

$$EA = arc\ \ tan\left(\frac{2 * aVF}{1 * \sqrt{3}}\right)$$

where aVF is the maximum QRS deflection in lead aVF, I is the maximum QRS deflection in lead I.

ECG criteria for left ventricular hypertrophy (ECG-LVH criteria):

- The Sokolow–Lyon index for left ventricular hypertrophy (SL-LVH) calculated as a sum of V1 and RV5 or V6 [14];
- The Cornell voltage calculated as a sum of RaVL and SV3 [15];
- The Gubner criterion, calculated as a sum of RI and SIII [16].

ECG criteria for right ventricular hypertrophy (ECG-RVH criteria):

- The Sokolow–Lyon criterion for right ventricular hypertrophy (SL-RVH), calculated as a sum of RV1 and SV5 (or V6) [14];
- Butler-Leggett formula (B-L), calculated as sum of R (or R′) V1 (or V2) and S I (or V6) minus SV1 [17].

Intraventricular conduction impairment:

- Fragmented QRS (fQRS): Additional R′, notching of the R or S wave [18];
- Slurring/bumps of R or S waves.

Statistics

The results are presented as mean ± SD for variables that were normally distributed, and as median (25%, 75%) for variables that were not normally distributed. For comparison of the means of normally distributed data one-way analysis of variance (ANOVA) was used, with the Tukey test for pairwise multiple comparison procedures. For comparison of the non-normally distributed data, ANOVA on ranks was used with the Dunn test for pairwise multiple comparison procedures. The prevalence of various variables was compared using the χ^2-test.

Because of differences in baseline characteristics between groups, the differences in QRSmax and electrical axis were tested using multivariate analysis by means of the general linear model (GLM), using age, BMI, blood pressure, and serum glucose level as covariates, gender and the group as fixed factors. Analyses were conducted using SPSS for Windows software (version 16.0). A p value < 0.05 was considered statistically significant.

Results

One hundred and ninety three subjects (137 men, 56 women; mean age 53.8 ± 11.2 years) who underwent sleep studies over a 3-year period met the inclusion criteria. Twenty two participants did not suffer from OSA (no OSA group), mild OSA was diagnosed in 46, moderate OSA in 26, and severe OSA in 99 patients.

Table 1 presents the basic characteristics and polysomnographic findings of the study population.

The proportion of males was higher in more severe OSA groups, the patients with more severe OSA were older, with higher values of BMI, diastolic and systolic blood pressure, and serum glucose and triglycerides levels. The proportion of subjects treated for arterial hypertension and for type 2 diabetes increased from no OSA to mild-moderate OSA and severe OSA group. The mean sleep SaO_2 and the minimum sleep SaO_2 decreased, whereas arousal index increased from no-OSA to mild-moderate and severe OSA group ($p < 0.001$ for all).

ECG parameters

Illustrative electrocardiograms of patients with severe OSA are shown in Fig. 1. There was a spectrum of QRS patterns, however the results revealed some common characteristics.

The QRS voltage was low in all groups. The QRSmax values decreased with OSA severity, the difference between no OSA and severe OSA groups was statistically significant ($p < 0.05$). The EA values were gradually shifted to the left (Fig. 2), with significant difference between moderate and severe OSA groups as compared to no OSA group ($p < 0.05$ for both). QRSmax and EA values did not correlate either with BMI, or with AHI.

In the general linear model, QRSmax was independently associated with age and the interaction between gender and OSA severity ($p = 0.001$, and $p = 0.004$, respectively; adjusted $R^2 = 0.178$). The electrical axis was found to be independently associated with OSA severity and age ($p = 0.037$, and $p = 0.026$, respectively; $R^2 = 0.109$).

12-lead ECG

The changes in QRSmax and EA were reflected in the values of maximum QRS deflections of 12-lead ECG leads (Fig. 3A and B). The QRS voltage increased in leads reflecting the shift of the electrical axis to the left, i.e. in aVL and I, while decreased significantly in leads II and aVF. The QRS voltage in precordial

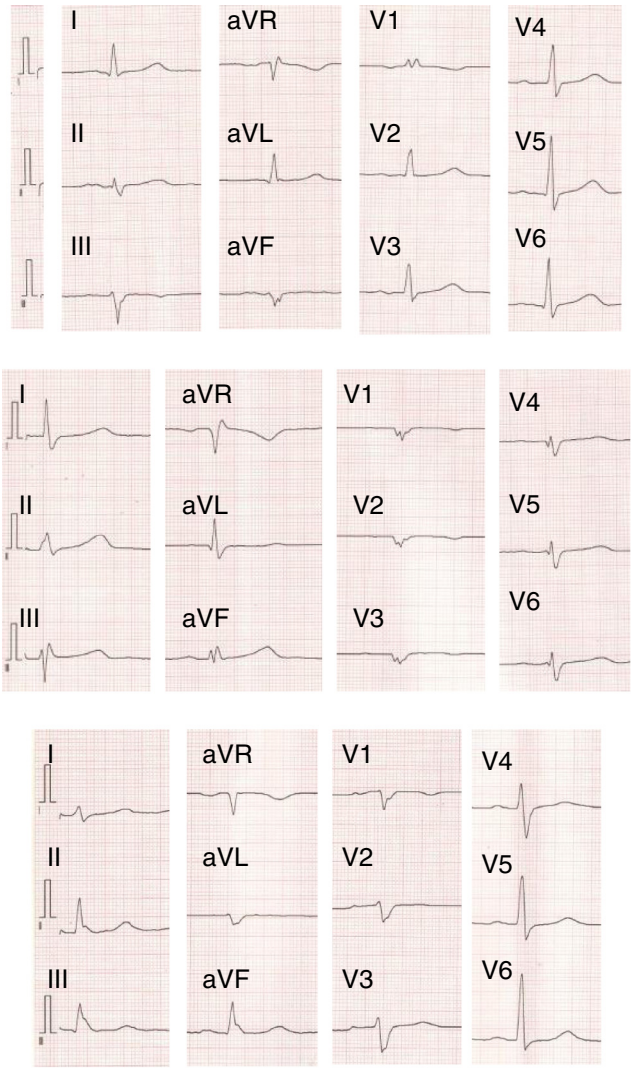

Fig. 1. Three electrocardiograms illustrating intraventricular conduction defects in patients with severe OSA.

leads decreased, and there was a significant difference in lead V1 in the severe OSA group as compared to non-OSA group.

ECG LVH/RVH criteria

We observed low occurrence of ECG-LVH criteria (Gubner: 0, 4.2, 3.7, and 5%, respectively; Cornell 0, 4.2, 3.7, and 8.1%, respectively; SL-LVH: 1, 0, 0, and 1%, respectively). The values of SLI-LVH decreased; the difference between no OSA and severe OSA groups was statistically significant (Fig. 4). The increase in ECG-LVH values was observed in those criteria that reflect left axis deviation: Gubner and Cornell criteria. The occurrence of RVH criteria was also low (SL-RVH: 9.1, 15.2, 14.8, and 19.8%, respectively; B-L: 4.5, 0, 6.4, and 8.9%, respectively). No statistical difference in ECG-RVH values between groups was observed.

Fragmented QRS

The proportion of patients with fQRS was considerably higher in all OSA groups as compared to the no OSA group (80% and 60%, respectively). However, the average number

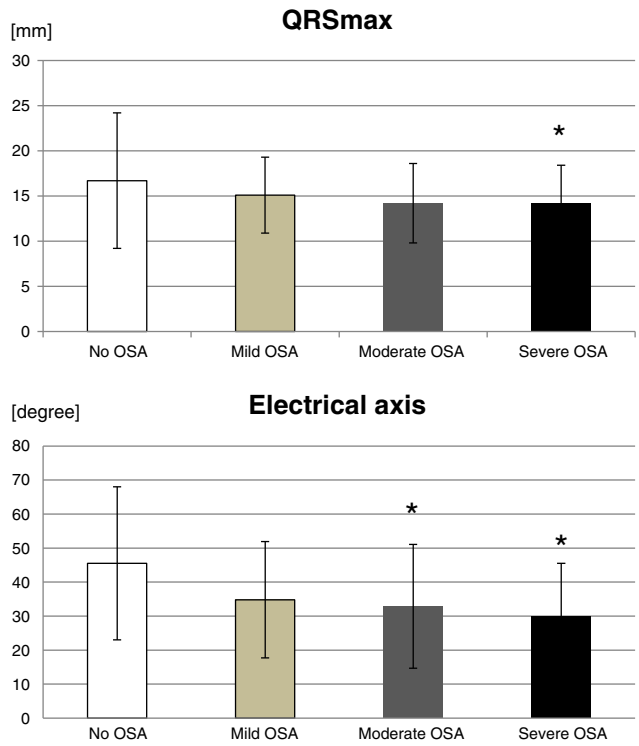

Fig. 2. Values of the maximum QRS spatial vector magnitude (QRSmax) and the electrical axis (EA).*$p < 0.05$ as compared to the no OSA group.

of affected leads per patient was lower in OSA groups (7.0; 3.4; 3.5; and 3.0, respectively).

Discussion

The main findings in this study were a gradual shift of the electrical axis to the left related to OSA severity; the QRSmax values were low in all patient groups, with a significant difference between no OSA and severe OSA groups. These changes were reflected in corresponding changes in the amplitude of 12-lead ECG and in low occurrence of ECG-LVH and ECG-RVH criteria. The OSA groups had higher occurrence of fQRS/bumps as compared to the no OSA group.

We observed a gradual significant shift of the electrical axis to the left in OSA patient groups related to OSA severity. The left axis deviation itself is an ECG abnormality predicting cardiovascular morbidity and mortality [19]. The shift of electrical axis to the left has been described in LVH [20,21], it is also seen in obese subjects [22,23]. However, in this study the effect of BMI or blood pressure on EA was not significant. The leftward shift of EA was associated with the OSA group and age, where age could imply not only age related degenerative changes but also duration of the pathological process related to OSA.

The leftward shift of the electrical axis in OSA patients was combined with low QRSmax values in all groups. In obese people, the low QRS voltage is attributed usually to obesity [24]. In this study, a significant difference in QRSmax was observed between no OSA and severe OSA groups. However, the multivariate analysis showed that

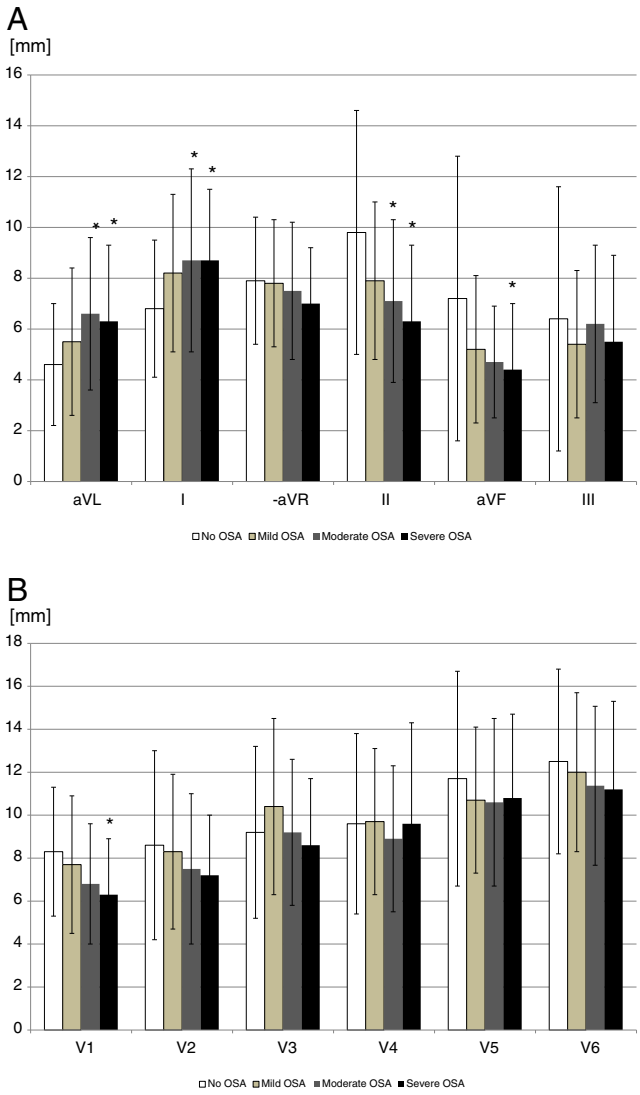

Fig. 3. Values of maximum QRS complex deflections in the standard 12-lead ECG.A: limb leads in Cabrera sequence.B: precordial lead.*$p < 0.05$ as compared to the no OSA group.

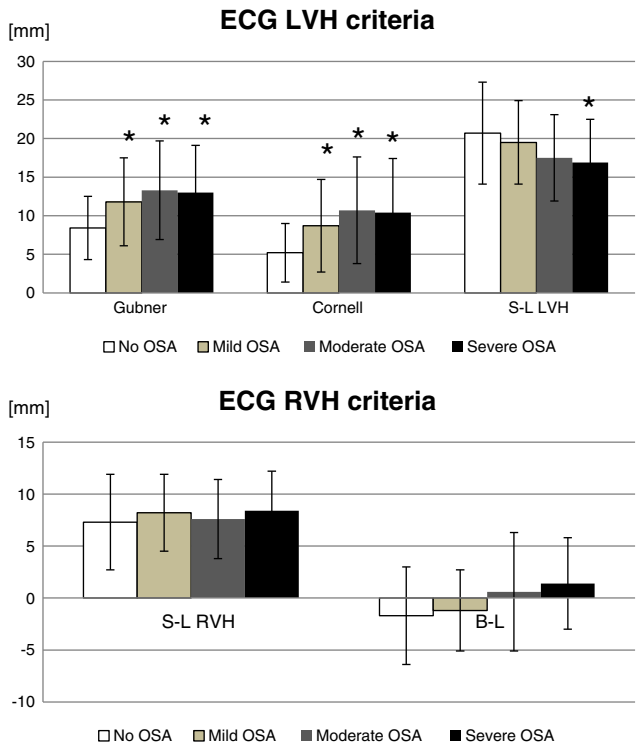

Fig. 4. Values of ECG criteria for left ventricular hypertrophy (ECG-LVH) and right ventricular hypertrophy (ECG-RVH).S-L LVH: Sokolow–Lyon criterion for left ventricular hypertrophy.S-L RVH: Sokolow–Lyon criterion for right ventricular hypertrophy.B-L: Butler–Leggett criterion for right ventricular hypertrophy.

QRSmax was associated with the OSA group and the interaction between gender and age, the effect of BMI was not significant. Furthermore, the effect of obesity on the QRS voltage is not that straightforward, and there is conflicting evidence regarding the QRS amplitude recorded in obese subjects. Frank et al. [23] reported the presence of low QRS voltage in only 3.9% of obese patients and QRS voltage increasing with increasing obesity, and vice versa a decrease in QRS voltage is reported in obese subjects after weight loss [25,26].

As mentioned above, in this study the low QRS voltage was combined with a leftward shift of electrical axis. In our previous study [12] we found this combination of decreased QRS voltage and leftward shift of electrical axis in patients with diabetes mellitus and metabolic syndrome, and a similar, less pronounced but significant trend in clinically healthy offspring of patients with diabetes mellitus and metabolic syndrome. We concluded that these changes in ECG pattern could be indicative of electrical remodeling of myocardium in DM and MetS patients. This conclusion was based on considering the complex structural and functional remodeling of myocardium documented in DM and MetS [27,28] and on the results of our simulation study showing a decrease in QRS voltage and left axis deviation in reduced intercellular coupling [10].

The changes in electrical axis and QRSmax were reflected in corresponding changes in low amplitude of 12-lead ECG and consequently in low occurrence of ECG-LVH and ECG-RVH criteria. These findings are in contrast with higher occurrence of LVH and/or RVH found by echocardiography in OSA patients [29–35]. Only small proportion of patients had ECG-LVH signs, although patients with severe OSA had significantly higher BP values and higher occurrence of hypertension. The occurrence of ECG-LVH slightly increased up to 7%, but only in those criteria, where the leftward shift of EA was reflected, i.e. in Gubner and Cornell criteria. It follows, that the increase in these two criteria was not primarily caused by an increased extent of activation front, but by a changed sequence of activation. Similarly, the occurrence of ECG-RVH criteria was low and the occurence of ECG-RVH did not differ between the groups what contrasts with published evidence of RVH detected by echocardiography in OSA patients [32–34].

The design of this study does not provide an explanation for this observation. It could be only speculated that the small proportion of ECG-LVH and ECG-RVH signs could be explained by the attenuating effect of obesity on the QRS voltage in combination with the structural and electrical remodeling of myocardium that counterbalance the effect of

increased ventricular mass [36]. OSA leads to structural and functional remodeling of myocardium, in severe OSA associated with global left ventricular dysfunction [37]. OSA itself causes a complex impairment of myocardium through multifactorial mechanisms: hypoxia, hypercapnia, inflammation, autonomic alteration and negative intrathoracic pressure. These mechanisms lead to ventricular hypertrophy and dysfunction at the organ level, presented at the tissue and cellular levels as multifocal infarcts, myocyte hypertrophy and apoptosis, inflammatory infiltrations, etc. [38]. OSA is recognized as a risk factor for arterial hypertension [5,39], stroke [40], myocardial ischemia [41], and diabetes [42]. The associated comorbidities have additional effect (obesity, lipotoxicity, diabetes, glucose and energy metabolism) [27,28,43,44]. It could be assumed that the ECG reflects interplay of all of these factors.

The assumption, that the myocardium is considerably affected is supported by the finding of fQRS in all groups. The proportion of patients with fQRS/bumps was significantly higher in OSA groups up to 84.6%; but the average number of affected leads was lower as compared to the no OSA group (about half of the no OSA patients).

The significantly higher number of OSA patients having fQRS is understandable. Fragmented QRS complexes are markers of depolarization abnormality and a predictor of cardiovascular death in patients with structural heart disease [45]. It is assumed that fQRS reflects disordered electrical activation of ventricles through inhomogeneous substrate, localized intramyocardial/intraventricular conduction blocks [6,45]. Abnormal impulse conduction creates a milieu for ventricular arrhythmias including fatal re-entrant ventricular tachyarrhythmias. This assumption is consistent with the published evidence of cardiac arrhythmias and conduction disturbances documented in OSA patients [46,47].

Of interest was the lower average number of affected leads per patient in OSA patients, as compared to no OSA patients. This finding could be possibly related to the small number of patients in some groups and will need further observations.

All patients with moderate and severe OSA underwent continuous positive airway pressure (CPAP) titration and were offered CPAP therapy for their OSA. It is known that possible remodeling can be affected by CPAP [2,34]. Nevertheless, the follow-up on the potential effects of CPAP therapy on QRS morphology was beyond the scope of the present study. Therefore, the potential to reverse myocardial remodeling by alleviation of OSA using noninvasive ventilation needs to be addressed by further studies.

In this study we found a combination of QRS complex changes in OSA patients: a leftward shift of EA, low QRS voltage and fragmented QRS, and we suppose that they indicated severity of myocardial alteration. This assumption is in agreement with findings of severe asynergy in patients having left-axis deviation, low voltage and QRS notching [48].

The QRS complex amplitude and electrical axis changes observed in this study were mostly within traditional normal ECG limits. Our results indicate that changes which are "within normal limits" may have clinical significance, and deserve more attention by clinicians and investigators.

Limitation of the study

First, the cross-sectional nature of the study design does not prove causation for the relationships between OSA, electrical remodeling and QRS morphology. Second, we did not assess echocardiographic signs of structural remodeling, and thus the relationships between ECG and morphologic findings remain to be explored in the future. Third, individuals with suspected OSA referred to the sleep laboratory are a discrete group and results obtained may potentially not be generalized. Also, the subgroup of subjects with no OSA was rather small and, therefore, further investigations in large cohorts are needed to analyze the effects of OSA on electrical remodeling and QRS morphology in more detail. On the other hand, studying a well-defined cohort of subjects who all underwent full polysomnography represents one of the main strengths of this study. In this study we used approximated QRS spatial vector magnitude (QRSmax) from the standard 12-lead ECG. We are aware of the limitation of this rough estimation; however, we wanted to estimate the spatial parameters of the cardiac electric field using data available in clinical practice.

Conclusions

In the present study we observed a leftward shift of EA, low QRS voltage and fragmented QRS in patients with OSA suggestive of myocardial alterations and electrical myocardial remodeling.

Acknowledgment

Supported by the grant APVV-0134–11: Effects of Hypoxia on Molecular Pathways related to Increased Cardiovascular Risk in Patients with Sleep Apnea and their Reversal by Therapy (HICART), Slovak Republic. We thank Julia Horilova for her assistance with statistical analysis.

References

[1] Levy P, Tamisier R, Arnaud C, Monneret D, Baguet JP, Stanke-Labesque F, et al. Sleep deprivation, sleep apnea and cardiovascular diseases. Front Biosci (Elite Ed) 2012;4:2007–21.

[2] Baranchuk A. Sleep apnea, cardiac arrhythmias, and conduction disorders. J Electrocardiol 2012;45:508–12.

[3] Roche F, Xuong AN, Court-Fortune I, Costes F, Pichot V, Duverney D, et al. Relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance. Pacing Clin Electrophysiol 2003;26:669–77.

[4] Shahar E, Whitney CW, Redline S, Newman AB, Nieto FJ, O'Connor GT, et al. Sleep disordered breathing and cardiovascular diseases: cross-sectional results of the Sleep Heart Health Study. Am J Respir Care Med 2001;263:19–25.

[5] Tkacova R, McNicholas WT, Javorsky M, Fietze I, Sliwinski P, Parati G, et al. European Sleep Apnoea Database study collaborators: nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. Eur Respir J 2014;44:931–41.

[6] Jain R, Singh R, Yamini S, Das MK. Fragmented ECG as a risk marker in cardiovascular diseases. Curr Cardiol Rev 2014;10:277–86.

[7] Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. Curr Opin Cardiol 2010;25:59–64.

[8] Gupta S, Cepeda-Valery B, Romero-Corral A, Shamsuzzaman A, Somers VK, Pressman GS. Association between QRS duration and obstructive sleep apnea. J Clin Sleep Med 2012;8:649–54.

[9] Bacharova L, Szathmary V, Kovalcik M, Mateasik A. Effect of changes in left ventricular anatomy and conduction velocity on the QRS voltage and morphology in left ventricular hypertrophy: a model study. J Electrocardiol 2010;43:200–8.
[10] Bacharova L, Mateasik A, Krause R, Prinzen F, Auricchio A, Potse M. The effect of reduced intercellular coupling on electrocardiographic signs of left ventricular hypertrophy. J Electrocardiol 2011;44:571–6.
[11] Bacharova L, Szathmary V, Mateasik A. QRS complex and ST segment manifestations of ventricular ischemia: the effect of regional slowing of ventricular activation. J Electrocardiol 2013;46:497–504.
[12] Bacharova L, Krivosikova Z, Wsolova L, Gajdos M. Alterations in the QRS complex in patients with metabolic syndrome and diabetes mellitus and in their offspring: early evidence of cardiovascular pathology. J Electrocardiol 2012;45:244–51.
[13] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. American Academy of Sleep Medicine: rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;15:597–619.
[14] Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar and limb leads. Am Heart J 1949;37:161–86.
[15] Casale P, Devereux R, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol 1985;6:572–80.
[16] Gubner RS, Ungerlieder HE. Electrocardiographic criteria of left ventricular hypertrophy: factors determining the evolution of the electrocardiographic patterns in hypertrophy and bundle branch block. Arch Intern Med 1943;72:196–209.
[17] Buttler PM, Leggett SI, Howe CM, Freye CJ, Hindman NB, Wagner GS. Identification of electrocardiographic criteria for diagnosis of right ventricular hypertrophy due to mitral stenosis. Am J Cardiol 1986;57:639–43.
[18] Kadi H, Kevser A, Ozturk A, Koc F, Ceyhan K. Fragmented QRS complexes are associated with increased left ventricular mass in patients with essential hypertension. Ann Noninvasive Electrocardiol 2013;18:547–54.
[19] Rabkin SW, Mathewson FAL, Tate RB. The electrocardiogram in apparently healthy men and the risk of sudden death. Br Heart J 1982;47:546–52.
[20] Stern S, Sclarowsky S. The ECG in diabetes mellitus. Circulation 2009;120:1633–6.
[21] Uusitupa M, Mustonen J, Siitonen O, Pyörälä K. Quantitative electrocardiographic and vectorcardiographic study on newly-diagnosed non-insulin-dependent diabetic and non-diabetic control subjects. Cardiology 1988;75:1–9.
[22] Zack PM, Wiens RD, Kennedy HL. Left-axis deviation and adiposity: the United States Health and Nutrition Examination Survey. Am J Cardiol 1984;53:1129–34.
[23] Frank S, Colliver JA, Frank A. The electrocardiogram in obesity: statistical analysis of 1,029 patients. J Am Coll Cardiol 1986;7:295–9.
[24] Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelfi WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. Circulation 1990;81:815–20.
[25] Eisenstein I, Edelstein J, Sarma R, Sanmarco M, Selvester RH. The electrocardiogram in obesity. J Electrocardiol 1982;15:115–8.
[26] Brohet CR, Tuna N. Quantitative analysis of the vectorcardiogram in obesity. J Electrocardiol 1975;8:1–11.
[27] Iozzo P. Metabolic toxicity of the heart: insights from molecular imaging. Nutr Metab Cardiovasc Dis 2010;20:147–56.
[28] Guzzardi MA, Iozzo P. Fatty heart, cardiac damage, and inflammation. Rev Diabet Stud 2011;8:403–17.
[29] Pujante P, Abreu C, Moreno J, Barrero EA, Azcarate P, Campo A, et al. Obstructive sleep apnea severity is associated with left ventricular mass independent of other cardiovascular risk factors in morbid obesity. J Clin Sleep Med 2013;9:1165–71.
[30] Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. Chest 2003;124:594–601.
[31] Zhang M, Li L, Fowler D, Zhao Z, Wei D, Zhang Y, et al. Causes of sudden death in patients with obstructive sleep apnea. J Forensic Sci 2013;58:1171–4.
[32] Sajkov D, McEvoy RD. Obstructive sleep apnea and pulmonary hypertension. Prog Cardiovasc Dis 2009;51:363–70.
[33] Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. Chest 1995;107:1538–44.
[34] Shivalkar B, Van de Heyning C, Kerremans M, Rinkevich D, Verbraeken J, De Backer W, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effect of treatment with continuous positive airway pressure. J Am Coll Cardiol 2006;47:1433–9.
[35] Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest 2007;131:1379–86.
[36] Bacharova L, Estes EH, Bang LE, Hill JA, Macfarlane PW, Rowlandson I, et al. Second statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. J Electrocardiol 2011;44:568–70.
[37] Varol E, Akcay S, Ozaydin M, Ozturk O, Cerci SS, Sahin U. Influence of obstructive sleep apnea on left ventricular mass and global function: sleep apnea and myocardial performance index. Heart Vessels 2010;25:400–4.
[38] Farré R, Montserrat JM, Navajas D. Morbidity due to obstructive sleep apnea: insights from animal models. Curr Opin Pulm Med 2008;14:530–6.
[39] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
[40] Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005;172:1447–51.
[41] Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002;166:159–65.
[42] Kent BD, Grote L, Ryan S, Pepin JL, Bonsignore MR, Tkacova R, et al. Diabetes mellitus prevalence and control in sleep disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest 2014;146:982–90.
[43] Iozzo P. Myocardial, perivascular, and epicardial fat. Diabetes Care 2011;34(Suppl 2):S371–9.
[44] Cao DJ, Gillette TG, Hill JA. Cardiomyocyte autophagy: remodeling, repairing, and reconstructing the heart. Curr Hypertens Rep 2009;11:406–11.
[45] Hayashi T, Fukamizu S, Hojo R, Komiyama K, Tanabe Y, Tejima T, et al. Fragmented QRS predicts cardiovascular death of patients with structural heart disease and inducible ventricular tachyarrhythmia. Circ J 2013;77:2889–97.
[46] Leung RS. Sleep-disordered breathing: autonomic mechanisms and arrhythmias. Prog Cardiovasc Dis 2009;51:324–38.
[47] Gami AS, Olson EJ, Shen WK, Wright RS, Ballman KV, Hodge DO, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol 2013;62:610–6.
[48] Bär FW, Brugada P, Dassen WR, van der Werf T, Wellens HJ. Prognostic value of Q waves, R/S ratio, loss of R wave voltage, ST-T segment abnormalities, electrical axis, low voltage and notching: correlation of electrocardiogram and left ventriculogram. J Am Coll Cardiol 1984;4:17–27.